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(54) Formulations for the topical delivery of avermectins

(57) A topical pour-on formulation containing an avermectin compound as the active ingredient an an alcohol soap tincture provides unexpectedly enhanced penetration of the active compound. The formulation preferably contains the avermectin ingredient and at least 50% soap tincture. The alcohol soap tincture may be green soap, alkali-metal-ammonium or metallic soaps, alkyl sulphates or potassium oil soaps with ethanol, methanol or isopropanol.

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TITLE OF THE INVENTION**FORMULATIONS FOR THE TOPICAL DELIVERY OF
AVERMECTINS****5 BACKGROUND OF THE INVENTION**

This invention relates to pharmaceutical compositions containing a vehicle which significantly enhances the transdermal delivery of avermectin and avermectin-like compounds across the skin of humans and animals (e.g. cattle, swine).

10 Avermectin compounds are known highly potent, antiparasitic, insecticidal, and anthelmintic agents, which are largely administered orally or parenterally. See for example U.S. Pat. Nos. 4,310,519, which reveals the natural product avermectins {formerly referred to as C-076 compounds} and 4,199,569, which reveals the
15 22,23-dihydro avermectin compounds. Avermectin compounds are administered topically also, however, the conventional vehicles used to carry the compounds, such as propylene glycol have provided at best only minimal permeation of the avermectin compounds.

20 Additionally, various risks and inconveniences associated with oral treatments or treatment by injection, such as gastrointestinal irritation resulting from exposing the gastrointestinal tract to pharmaceutical preservatives, tableting agents and the like, have lead to a growing desire to develop a more effective and convenient method for
25 externally administering the avermectin compounds.

Transdermal delivery of avermectins is desirable because the skin is very accessible, has a large surface area and provides a non-invasive, rapid and easy method of treatment. Moreover, dermal application avoids the risk of trauma and inhalation pneumonia associated with oral drenching or local reaction at injection sites.

30 Because the skin is highly impermeable for many compounds, in particular large molecules, a vehicle system with permeation enhancing characteristics in which the drug of interest must be soluble is required for its dermal delivery. The vehicles employed for enhanced penetration across the skin are numerous and vary in that

a vehicle that is an excellent carrier for one compound may not be for another. Conventional vehicles used in topical formulations for the delivery of avermectins have been solvents or mixtures of solvents in which the drug of choice dissolves easily and which may have some
5 penetration enhancing characteristics, e.g. glycols, fatty acids, fatty acid esters, fatty alcohols, triglycerides, alkanols, aromatic alcohols, sulfoxides, esters, ethers, and various saturated and unsaturated oils. For example, U.S. Patent No. 4,070,476 describes the use of dimethylsulfoxide and amyl alcohol mixture as carriers for passing
10 anthelmintic compounds through the skin. U.S. Patent No. 3,934,013 describes topical pharmaceutical compositions which contain at least two corticosteroids, propylene glycol, a fatty alcohol and water. U.S. Patent No. 4,070,462 teaches a topical vehicle which includes 5-15% 1,2-propanediol, 2,3-butanediol or 2-methyl-2,4, propanediol; 1-3%
15 propylene glycol monostearate; and petrolatums and waxes to 100%. U.S. Patent No. 4,070,462 discloses topical steroid compositions containing 6% propylene glycol and 1% propylene glycol monostearate.

The present invention is significantly different in that soap
20 tinctures are used as vehicles for superior transdermal delivery of avermectin and avermectin-like compounds.

SUMMARY OF THE INVENTION

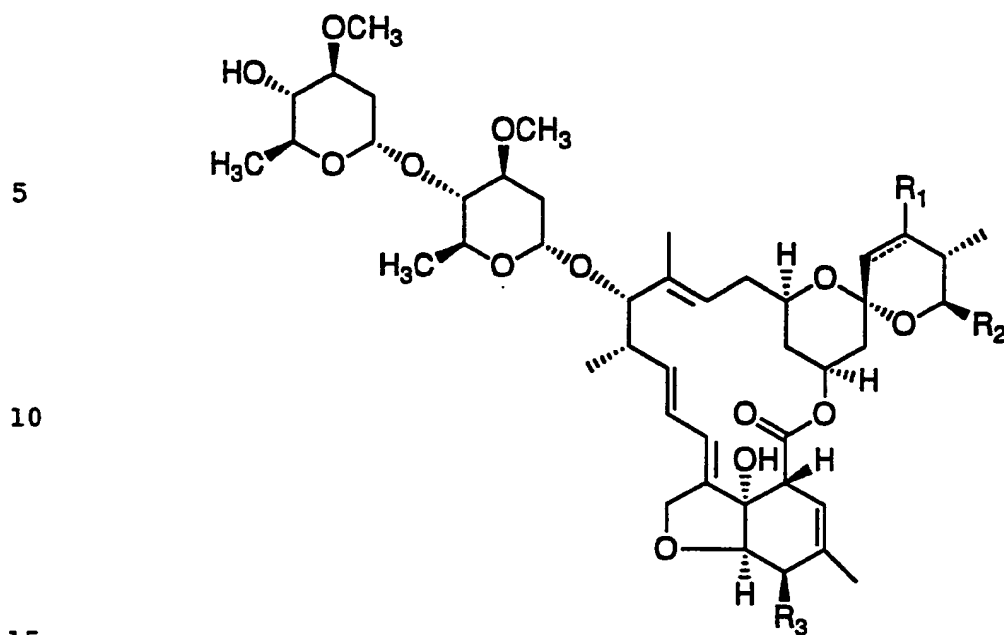
The present invention relates to a novel formulation for the transdermal delivery of avermectins which are potent antiparasitic,
25 insecticidal and anthelmintic agents used to combat parasitic diseases in animals. Topical delivery is accomplished by one of two ways. The first is by topically applying formulations containing a known amount of an avermectin compound and a soap tincture to the skin of an animal, whereby the soap tincture enhances the penetration of the compound of
30 interest into the skin and enters the systemic circulation. The second is by washing the skin of the animal with the soap tincture before the topical application of a formulation containing the avermectin active ingredient. The alcohol-based detergent unexpectedly operates to significantly enhance the penetration of the avermectin compound.

Accordingly, it is an object of this invention to describe such enhanced effect. An additional object is to describe the avermectin compounds which may be employed in the formulation. Another object is to describe the additional components which may employed in the formulation. Still another object of this invention is to provide a method of administering the formulation which contains the avermectin active ingredient. Additional objects of this invention will be apparent to persons of ordinary skill in the art upon reading the following detailed description and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

This invention consists of a topical pour-on formulation of soap tincture and an avermectin compound which has been found to considerably enhance penetration of the active ingredient to effectively combat against internal and external parasites of animals. Application of the soap tincture to the skin of the animal before applying any pour-on formulation containing an avermectin compound also operates to significantly enhance penetration of the active ingredient.

The avermectin compounds employed in the present invention are known potent antiparasitic agents against endoparasites and ectoparasites. Included within the scope of this invention are the commercially available avermectin and avermectin-like compounds, including those used as injectables or used orally, and any naturally occurring avermectin or derivative thereof. The basic naturally occurring avermectins are series of macrocyclic lactones which are substituted at position 13 with a disaccharide consisting of two oleandrose residues. See for example, U.S. Pat. No. 4,310,519. The preparation and properties of synthetic avermectin aglycones in which the disaccharide moiety has been removed leaving a free hydroxyl group at position 13 have been described by Mrozik et al., J. Org. Chem. **1982**, 47, 489-492 and by Chabala et al., J. Med. Chem. **1980**, 23, 1134-1136. The natural compounds have the following general structure:



wherein the broken line at the 22,23-position indicates a single or double bond and;

- 20
- R_1 is hydroxy and is present only when said broken line indicates a single bond;
- R_2 is isopropyl or sec-butyl; and
- R_3 is methoxy or hydroxy.

25 There are eight major natural avermectin compounds, designated A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. These designations are based on the structure of the individual compounds as shown in the following table (referring to the foregoing structural formula).

30

	<u>Compound</u>	<u>22,23-bond</u>	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>
5	A1a	double bond	---	sec-butyl	-OCH ₃
	A1b	double bond	---	isopropyl	-OCH ₃
	A2a	single bond	-OH	sec-butyl	-OCH ₃
	A2b	single bond	-OH	isopropyl	-OCH ₃
	B1a	double bond	---	sec-butyl	-OH
10	B1b	double bond	---	isopropyl	-OH
	B2a	single bond	-OH	sec-butyl	-OH
	B2b	single bond	-OH	isopropyl	-OH

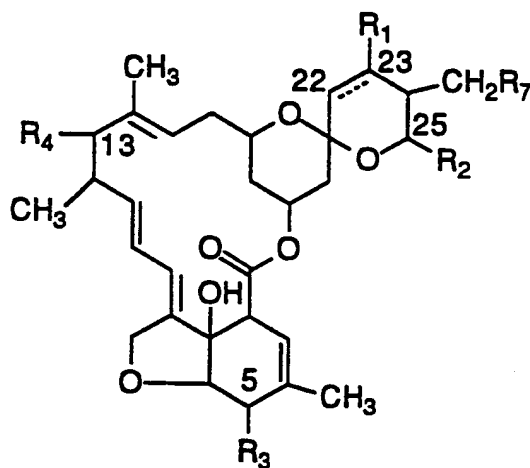
15 The avermectins are generally isolated as mixtures of the a
 and b components (typically $\geq 80\%$ a and $\leq 20\%$ b). Such compounds
 differ only in the nature of the R₂ substituent and this minor structural
 difference has been found to have very little effect on the chemical
 reactivity or biological activity of the compounds. Thus although the a
 and b components can be separated from each other by chromatography
 20 this is not necessary and hence is not normally done. The presence of a
 mixture of a and b components may be indicated by dropping the a or b
 from the designation of the compound. A mixture of avermectin B1a
 and avermectin B1b is thus referred to as avermectin B1. Alternatively
 a slash(/) is inserted between the compound designations to indicate a
 mixture such as in "B1a/B1b".

25 The above structural formula is shown without a definitive
 stereochemistry at certain positions and with a defined stereochemistry at
 other positions. However, during the course of the synthetic procedures
 used to prepare such compounds, or using racemization or
 30 epimerization procedures known to those skilled in the art, the products
 of such procedures can be a mixture of stereoisomers. In particular, the
 stereoisomers at the 13- and 23-positions may be oriented either α - or
 β - representing such groups being below or above the general plane of
 the molecule, respectively. In each such case, and at other positions

in the molecule, both the α - and β - configurations are intended to be included within the ambit of this invention.

A related family of natural products is known as the milbemycins. The milbemycins have the same macrocyclic ring structure as the avermectins but have no substitution at position 13 and have a methyl or ethyl group at position 25 (R_2 = methyl or ethyl rather than isopropyl or sec-butyl as in the avermectins). The milbemycins and the fermentation conditions used to prepare them are described in U.S. Pat. No. 3,950,360. Closely related 13-deoxyavermectin aglycones are prepared by chemical modification of the natural avermectins and have been described in U.S. Pat. Nos. 4,171,134 and 4,173,571.

The avermectin compounds useful in the present invention have the following structure:



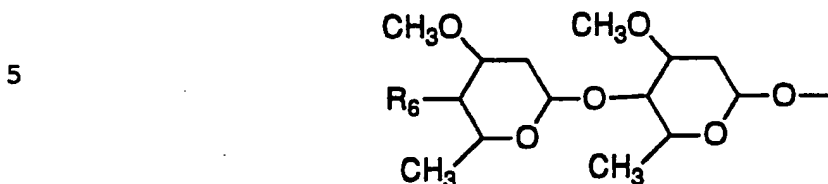
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

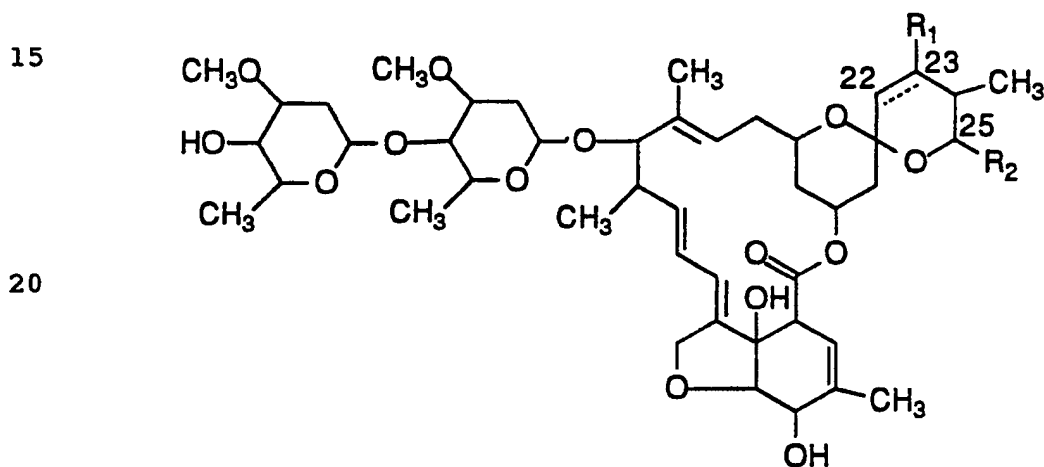
R_3 is hydroxy, methoxy or $=NOR_5$ where R_5 is hydrogen or lower alkyl;

R₇ is hydrogen, hydroxy, or lower alkyl; and
R₄ is hydrogen, hydroxy, polyalkoxy or



where R₆ is hydroxy, amino, mono- or di-loweralkylamino or
10 loweralkanolyamino.

The preferred compounds are 22,23-dihydro- avermectin
B1a/B1b (ivermectin), which are approved as broad spectrum
antiparasitic agents. The structure of ivermectin is as follows:



25 wherein for ivermectin the double bond represents a single bond and R₁
is hydrogen; and

R₂ is isopropyl or sec-butyl. Examples of avermectin
compounds useful in the present invention include, but are not limited
to:

- 30
- 22,23-dihydroavermectin B1a/B1b;
 - 22,23-dihydroavermectin B1a/B1b monosaccharide;
 - 24a-hydroxy-22,23-dihydroavermectin B1a/B1b;
 - 24a-hydroxy-22,23-dihydroavermectin B1a/B1b monosaccharide;

-4"-deoxy-4"-epi-methylamino-avermectin B1a/B1b;

-4"-epi-acetylamino-4"-deoxyavermectin B1a/B1b;

5 Mixtures of avermectins are also useful in the present invention. Additionally, other animal health products such as steroids, antibiotics, ectoparasitic agents and the like are useful in the present invention.

10 The present method is preferably applied to mammals, domestic or farm animals, such as sheep, pigs, domestic bovine animals (i.e., cattle), horses, goats, dogs and cats. It can also be applied to human beings as well as laboratory animals such as rats and guinea pigs. The present method may be used to inhibit infection or to treat an infection already present.

15 The dosage of the avermectin compound required for best results depends on several factors such as the species and size of the animal, the type and severity of the infection and the compound use. The formulation of the present invention may contain the soap tincture and the avermectin compound as the only ingredients. The formulations will generally be prepared to administer a safe and effective amount from 0.005 to 10% by weight of the avermectin component, preferably from 0.01 to 5% by weight. Most preferably a formulation containing about 1% of the avermectin is employed. At a preferred dose volume of about 1 ml to treat 50 kg of animal bodyweight the formulation contains from 5 to 50 mg of avermectin compound per ml of solution.

25 In addition to the soap tincture and the avermectin the formulation can contain an antioxidant such as a propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like. The antioxidants are generally added to the formulation at rates of from 0.005 to 1.0% (w/v).

30 The formulation can additionally be prepared by the addition of an additional soap tincture-soluble solvent such as glycols, triglycerides, esters, ethers, saturated and unsaturated oils and the like. The additional solvent can be added at volumes of up to 50% of the the volume of the soap tincture, preferably up to 25% of the volume of

soap tincture. The most preferred formulations consists of only the soap tincture, the avermectin and the antioxidant.

5 The formulation is prepared by dissolving the avermectin compound in approximately 80% of the intended volume of the soap tincture and then adjusting the volume to 100% by the addition of the final volume of soap tincture. The additional solvents and antioxidant may be combined with the soap tincture prior to mixing with the avermectin or added as the final volume of solvent.

10 In the present invention, the avermectin compounds penetration through the skin of various animals can be enhanced by one of two ways. The first is by washing the skin of the animal with the soap tincture before application of an avermectin formulation. Application of the formulation can occur from just prior to washing the skin with the soap tincture up to 48 hours after the washing. Any
15 commercially available topical avermectin formulation can be used including but not limited to Ivomec® and non-commercially available avermectin formulations such as,

20 Composition A

4"-epi-acetylamino-4"-deoxyavermectin B1 1.0% (w/v)
Lauroglycol/Miglyol*-840/ethanol/oleic acid
(4:1:3:2 by volume) q.s. 100% (w/v.)

25 *Miglyol-840= propylene diester of saturated fatty acids
(C8 to C10)

Composition B

30 4"-epi-acetylamino-4"-deoxyavermectin B1 1.0% (w/v)
Lauroglycol/docusate sodium (7:3 by volume) q.s. 100% (w/v.)
and the like.

 The second and preferred means of enhancing avermectin penetration is simply by using a pour-on formulation containing the avermectin compound and the alcohol soap tincture. The formulation may be a cream, however, a liquid composition is most preferred because it offers a convenient and accurate means of dose application.

Thus a suspension of the avermectin compound in a liquid vehicle is preferred.

The vehicle of the present invention is a soap tincture made from mixing detergents such as alkali-metal and ammonium soaps, metallic soaps, amine soaps, alkyl sulphates or sulphated fatty alcohols, alkyl ether sulphates, potassium oil soaps made from vegetable oils, oleic acid, potassium hydroxide, glycerol and water (most preferred), and the like, with alcohols such as isopropanol, methanol, ethanol, and the like, preferably ethanol. Use of the resulting soap tincture as a topical vehicle significantly enhances the dermal penetration of the avermectins. The detergents are known in the art and are readily available under a variety of proprietary names such as Green Soap, Soft Soap, Soft Soap Liniment etc... For instance, some of the Examples below are performed using a tincture of Green Soap (Harley Chemicals, Camden, NJ). The Green Soap tincture consists of the following:

Green Soap Tincture (% w/w)

Green Soap (63-67)

Alcohol (22-28)

Water (q.s. to 100)

ph (8 to 10)

The Green Soap is prepared by saponification of any suitable vegetable oil (excluding coconut oil and palm kernel oil), or oils or their fatty acids with potassium or sodium hydroxide (potassium hydroxide most preferable), oleic acid, glycerol and water in the following ratio:

Green Soap (% w/w)

Vegetable oil (35-50) Glycerol (5-7)

Oleic Acid (1.5-3) Water (q.s. to 100)

Potassium/Sodium hydroxide (7-10)

Examples of suitable vegetable oils are olive, soybean, sesame, safflower and the like. The soap is a soft substance with a

yellowish-white to light green or light brown transparent color, which generally is dyed to give a green color. Green Soap has been used for purposes such as to remove incrustations in chronic scaly diseases such as psoriasis and to cleanse the hands and scalp before application of lotions or before surgery, as an enema, as a mild counter-irritant which is used in the treatment of sprains and bruises and many other like purposes. It is to be understood that the tincture of Green Soap, while the most preferred alcohol based detergent, is only one of the many soap tinctures that can be employed in the present invention. See US Pharma. XXII Official Monograph pg. 615 and Reynolds. Soaps and other Anionic Surfactants, 29 Martindale the Extra Pharmacopoeia 1416 &6014-f (1989) for detailed method of preparing Green Soap and Green Soap tinctures and their uses.

EXAMPLE OF THE INVENTION

EXAMPLE 1

The formulations of this invention which are employed depend upon the particular avermectin compound and treatment. The avermectin is dissolved in approximately 80% of the soap tincture. When dissolved, the BHT is optionally added and dissolved. The volume is adjusted to 100% with soap tincture and the solution sterilized by membrane filtrations and packaged aseptically. The following are nonlimiting examples of the composition of the present invention, which are conventionally formulated by mixing all components as stated above:

Composition I

4"-deoxy-4"-epimethylaminoavermectin B1	0.5%(w/v)
BHT	0.01%(w/v)
Tincture of Green Soap	q.s 100.00%(w/v)

Composition II

	22,23-dihydroavermectin B1	1.0%(w/v)
	BHT	0.01%(w/v)
5	Olive Oil Soap Tincture	q.s 100.00%(w/v)

Composition III

	22,23-dihydroavermectin B1	1.0%(w/v)
	BHT	0.01%(w/v)
10	Soybean Oil Soap Tincture	q.s 100.00%(w/v)

Composition IV

	22,23-dihydroavermectin B1	1.0%(w/v)
	BHT	0.01%(w/v)
15	Sesame Oil Soap Tincture	q.s 100.00%(w/v)

Composition V

	22,23-dihydroavermectin B1	1.0%(w/v)
	BHT	0.01%(w/v)
20	Safflower Oil Soap Tincture	q.s 100.00%(w/v)

Composition VI

	4"-epi-acetylamino-4"-deoxyavermectin B1	1.0%(w/v)
	BHT	0.01%(w/v)
25	Tincture of Green Soap	q.s 100.00%(w/v)

Composition VII

	22,23-dihydroavermectin B1	1.0% (w/v)
30	Tincture of Green Soap	q.s 100.00% (w/v)

EXAMPLE 2

Compositions II to VI were studied in vitro as described below.

Penetration Studies

The following penetration studies demonstrate the penetration-enhancing capabilities of the soap tincture compositions and methods of the instant invention. These examples are used for the purpose of illustration only, and should not be considered limiting in any way the invention being disclosed here. These examples demonstrate the ability of the present invention to enhance the penetration of avermectin compounds when compared to commercially available IVOMECS[®] pour-on vehicle (80% isopropanol, 20% Crodamol CAP, 0.05% triethanolamine).

The penetration studies were carried out in the following manner. Franz diffusion cells (FDC-400, Crown Glass Co., Somerville, NJ) were modified to allow continuous, automated sampling for skin penetration experiments. Skin samples excised from cattle or swine were used. An aliquot of [³H] labelled avermectin compound was added to unlabelled avermectin solutions to give a final activity of about 0.7 μ Ci/ml for use in the donor cells. The volume of solutions deposited in donor compartment of the cells was 0.1ml. The effective diffusion area was 1.77cm². The water jacketed receptor compartment (12.2mL) was maintained at 37 to 39 \pm 1^oC and constantly stirred by a magnetic stirring bar. Receptor medium, 25% glycerol formal in water to maintain sink condition for avermectin compounds, was delivered at 0.5mL/hr by a peristaltic pump to a fraction collector. Samples so collected were assayed by a liquid scintillation counter. The penetrations studies were performed at room temperature.

The data represent the average of at least three independent measurements for each study. The term mcg= micrograms, 4"-deoxy'4"-epi-methylamino- avermectin B1= EPMA, 4"-epi-acetylamino-4"-deoxy- avermectin B1= EADA, 22,23-dihydroavermectin B1= DA, which is also the active ingredient in the commercially available IVOMECS® pour-on.

EXAMPLE 3

10

SWINE SKIN:

	Vehicle	mcg/cm ² (0-21 hr)	mcg/cm ² (0-45 hr)
	1.0% DA in IVOMECS® Pour-on	0.23	0.39
15	1.0% DA in tincture of Green Soap (Harley Chem.)	0.60	1.10
	1.0% DA in sesame oil soap tincture	0.40	0.85
	1.0% DA in safflower seed oil soap tincture	0.49	1.14
	1.0 DA in olive oil soap tincture	0.73	1.24
20	1.0% DA in soybean oil soap tincture	0.92	1.56

EXAMPLE 4

SWINE SKIN:

	Vehicle	mcg/cm ² (0-21 hr)	mcg/cm ² (0-45 hr)
25	1.0% EPMA in IVOMECS® Pour-on	0.61	0.97
	1.0% EPMA in tincture of Green Soap (Harley Chem.)	3.07	5.45
	1.0 EPMA in olive oil soap tincture	1.94	3.81
30	1.0% EPMA in soybean oil soap tincture	1.33	2.84

EXAMPLE 5

SWINE SKIN:

		mcg/cm ² (0-21 hr)	mcg/cm ² (0-45 hr)
5	Vehicle		
	1.0% EADA in IVOMECS® Pour-on	0.09	0.21
	1.0% EADA in tincture of Green Soap (Harley Chem.)	0.49	0.96
	1.0 EADA in olive oil soap tincture	0.73	1.50
10	1.0% EADA in soybean oil soap tincture	0.66	1.30

EXAMPLE 6

CATTLE SKIN

		mcg/cm ² (0-22 hr)	mcg/cm ² (0-46 hr)
15	Vehicle		
	1.0% EPMA in IVOMECS® Pour-on	1.67	2.53
	1.0% EPMA in tincture of Green Soap (Harley Chem.)	3.97	5.85
20	1.0 EPMA in olive oil soap tincture	8.17	10.97

EXAMPLE 7

CATTLE SKIN

		mcg/cm ² (0-22 hr)	mcg/cm ² (0-46 hr)
25	Vehicle		
	0.5% EPMA in tincture of Green Soap (Harley Chem.)	3.47	4.50
	0.5% EPMA in soybean oil soap tincture	2.43	3.52
30	0.5% EPMA in sesame oil soap tincture	2.45	3.66
	0.5% EPMA in olive oil soap tincture	1.74	2.91

EXAMPLE 8

5 The effect of washing the animals with the soap tincture
prior to topical administration of any avermectin formulation, including
commercially available avermectin formulations such as IVOMEC®, to
enhance their permeation and hence their bioavailability and efficacy
was shown to be significant. For example, six shoats were washed with
the tincture of Green Soap (Harley Chemical Co., Camden, NJ) a day
10 prior to topical administration of 4"-epi-acetylamino 4"-deoxy-
avermection B1 (EADA) in Lauroglycol/Miglyol-840/Ethanol/Oleic
acid (4:1:3:2 by volume) and Lauroglycol/Docusate sodium (7:3 by
volume) vehicles (Miglyol-840 is propylene diester of saturated fatty
acids). These formulations were applied with a dauber to the back of
the animals at a dose of 1.0 mg/kg bodyweight. Mean peak plasma
15 concentrations of ≈3.0 ng/ml at 24 hours post administration were
obtained. These values were substantially higher than those obtained
with EADA in IVOMEC® cattle pour-on vehicle (1.4 ng/ml). Efficacy
against both Ascaris suum and Trichuris suis was 100% with either
20 formulation.

EXAMPLE 9

25 The effect of washing the animals with the tincture of
Green Soap prior to topical administration of avermectins was also
demonstrated in vitro. This was done by exposing the skin on the
diffusion cells to the tincture of Green Soap followed by its removal and
application of 1.0% EADA in Lauroglycol/Miglyol-840/Ethanol/Oleic
acid (4:1:3:2 by volume), LGMEOA, to the skin.

30

Vehicle	mcg/cm ² (0-21 hr)	mcg/cm ² (0-45 hr)
1.0% EADA in LGMEOA	0.30	0.46
1.0% EADA in LGMEOA	0.54	1.34

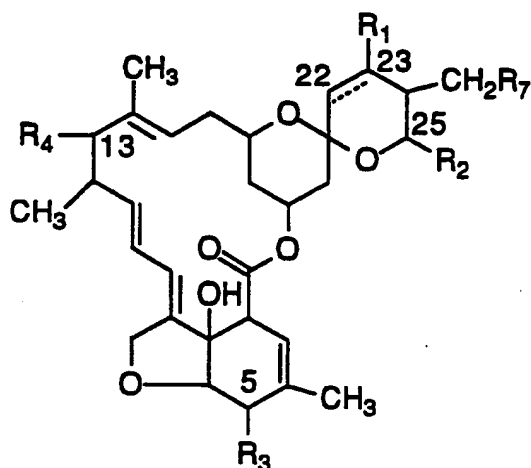
(prewashed with the tincture of Green Soap).

The instant invention provides treatment and prevention of parasitic conditions which respond to either local or systemic activity of avermectins. When local treatment, systemic treatment, or prevention
5 of disease is desired, the compositions of the present invention are applied to the localized area of inflammation or lesion. Treatments can also occur by a mechanical sustained release device or dressing such as a bandage is used to deliver the compounds systemically. See Johnson, J.C. et al., Sustained Release Medications, Chemical Technology Review
10 No. 177 pp. 82-113 (1980). Accordingly, this invention provides a method for treating and preventing endoparasitic diseases, generally referred to as helminthiasis, in domestic animals such as cattle, sheep, horses, dogs, cats, goats, swine, and poultry and in humans. The
15 present invention also provides a method for treating and preventing parasitic infections of the above animals by ectoparasites such as ticks, mites, lice, fleas and the like, which can lead to the transmission of serious diseases such as encephalitis, anaplasmosis, swine pox, and the like which can be fatal.

In accordance with the instant invention topical treatment
20 comprises applying the compositions containing a formulation of an avermectin compound as the active ingredient in an alcohol based detergent as the penetrating vehicle, to the skin, i.e., at the affected area or the desire area for systemic treatment or in the alternative, washing
25 the skin of the animal with the alcohol based detergent before applying a formulation containing an avermectin compound. The rate of application and duration of treatment depends on many factors, including the condition being treated, the area involved the physical
30 condition of the patient as well as other factors within the particular knowledge of the patient and/or physician/veterinarian.

WHAT IS CLAIMED IS:

1. A formulation consisting of a soap tincture and from 0.005 to 10% w/v of an avermectin compound having a structural formula:



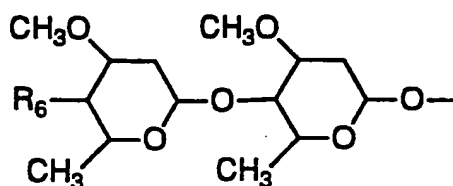
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

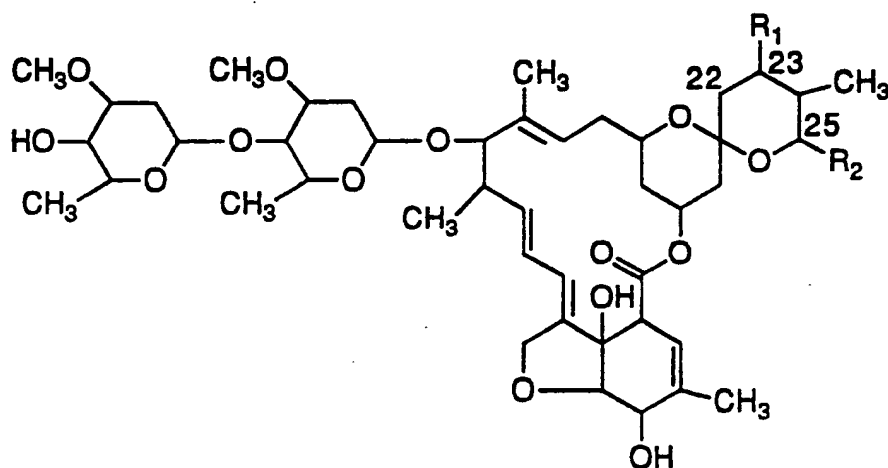
R_3 is hydroxy, methoxy or $=NOR_5$ where R_5 is hydrogen or lower alkyl;

R_7 is hydrogen, hydroxy or loweralkyl; and
 R_4 is hydrogen, hydroxy or



where R_6 is hydroxy, amino, mono- or di-loweralkylamino or loweralkanoylamino.

2. The formulation of Claim 1 wherein the avermectin compound is ivermectin having the formula:



wherein R_1 is hydrogen; and
 R_2 is isopropyl or sec-butyl.

3. The formulation of Claim 1 which contains from 0.01 to 5% w/v of the avermectin compound.

4. The formulation of Claim 1 wherein the alcohol soap tincture is Green Soap, alkali-metal soaps, ammonium soaps, metallic soaps, alkyl sulphates, potassium oil soaps and ethanol, methanol or isopropanol.

5. The formulation of Claim 4 wherein the soap tincture is Green Soap and ethanol.

6. The formulation of Claim 1 which also contains an antioxidant at from 0.005 to 1% w/v.

7. The formulation of Claim 6 wherein the antioxidant is n-propyl gallate, BHA, BHT or monothioglycerol.

5 8. The formulation of Claim 7 wherein the antioxidant is BHT.

9. The formulation of Claim 1 which also contains an additional solvent which is propylene glycol, triglycerides, fatty acids, fatty alcohols, fatty acid esters, esters, ethers, unsaturated oils or
10 saturated oils and which is present at up to 50% w/v.

10. The formulation of Claim 9 wherein the additional solvent is present at up to 25% w/v.

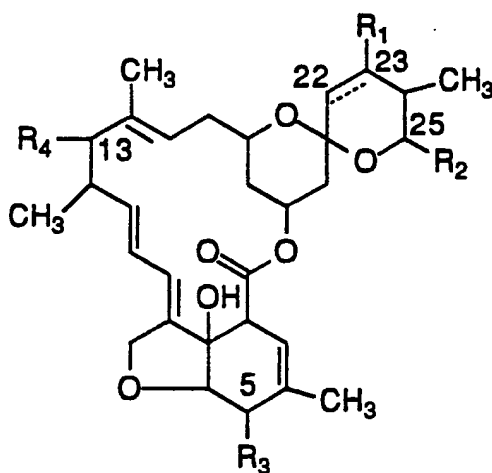
15 11. A process for the preparation of the formulation of Claim 1 which comprises dissolving the avermectin compound in about 80% of the volume of the soap tincture and adding as a final volume, the remainder of the alcohol soap tincture; and sterilizing the resultant
20 formulation.

12. The process of Claim 11 wherein the additional solvents and antioxidant may be combined with the soap tincture prior to mixing with the avermectin or added as the final volume of solvent or additive.
25

13. A method for the treatment and prevention of internal and external parasites of animals, which comprises topically applying to the skin of the animal the formulation of Claim 1.

30 14. A method for the treatment and prevention of internal and external parasites of animals which comprises washing the skin of animals with the soap tincture of Claim 4 before topically applying a liquid formulation containing an avermectin compound.

15. A method according to Claim 14 wherein the topical avermectin formulation consists of any topical avermectin formulations including IVOMEC® or a soap tincture or a mixture of Lauroglycol/triglyceride/ethanol/oleic acid (4:1:3.2 by volume),
 5 Lauroglycol/docusate sodium (7:3 by volume), or combination thereof, and 0.005 to 10% w/v of an avermectin compound having the formula:



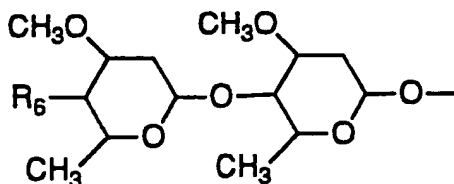
20 where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

25 R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

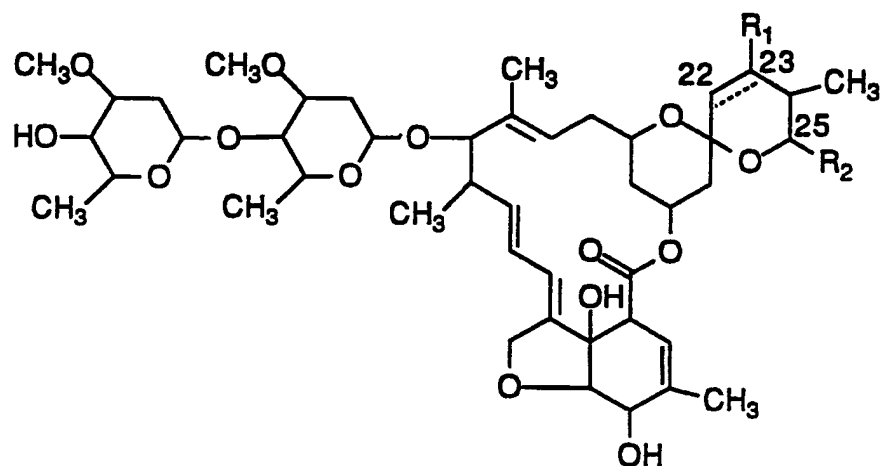
R_3 is hydroxy, methoxy or =NOR₅ where R₅ is hydrogen or lower alkyl; and

R_4 is hydrogen, hydroxy, polyalkoxy or



where R₆ is hydroxy, amino, mono- or di-loweralkylamino or loweralkanoylamino.

16. The formulation of Claim 15 wherein the avermectin compound has the formula:



wherein for ivermectin the double bond represents a single bond and R₁ is hydrogen; and
R₂ is isopropyl or sec-butyl.

Relevant Technical Fields

(i) UK Cl (Ed.M) A5B (BHA, BJB, BKA, BKB)

(ii) Int Cl (Ed.5) A61K 9/08, 31/35

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: DIALINDEX (VETSCI, WPI MEDICINE) CAS-ONLINE

Search Examiner
J F JENKINS

Date of completion of Search
6 MAY 1994

Documents considered relevant following a search in respect of Claims :-
1 to 12 and 16

Categories of documents

- | | |
|---|---|
| X: Document indicating lack of novelty or of inventive step. | P: Document published on or after the declared priority date but before the filing date of the present application. |
| Y: Document indicating lack of inventive step if combined with one or more other documents of the same category. | E: Patent document published on or after, but with priority date earlier than, the filing date of the present application. |
| A: Document indicating technological background and/or state of the art. | &: Member of the same patent family; corresponding document. |

Category	Identity of document and relevant passages	Relevant to claim(s)
A	US 4389397 (LO ET AL) see Examples	
A	EP 0146414 A2 (MERCK & CO) see Examples and Claims	

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